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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,958	02/03/2004	Robert Charles Downs	P1008US11	3828
29490 7590 05/29/2008 GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION 10675 JOHN JAY HOPKINS DRIVE, SUITE E225 SAN DIEGO, CA 92121-1127				
			EXAMINER BOWERS, NATHAN ANDREW	
			ART UNIT 1797	PAPER NUMBER
			NOTIFICATION DATE 05/29/2008	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPLegal@gnf.org

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Office Action Summary

Application No.

10/771,958

Applicant(s)

DOWNS ET AL.

Examiner

NATHAN A. BOWERS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 March 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-79 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42-79 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SG/US)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 42, 43, 48-51, 59-62, 64-67 and 77-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitzman (US 4519984) in view of Muth (DE 19712575) and/or Weuster-Botz (US 6063618).

With respect to claims 42 and 59-61, Hitzman discloses a method of fermenting a plurality of samples by providing a plurality of sample vessels (Figure 2:52) in a container frame (Figure 2:54). Fermenting is accomplished in part by simultaneously delivering gas to each of the sample vessels using a plurality of cannulas (Figure 1:18) associated with the sample vessels. Each of the cannulas is associated with a fermenter head (Figure 2:60) that comprises a manifold through which air is dispersed from a common source to the individual cannulas that are in communication with a specific vessel. This is described in column 2, line 51 to column 3, line 60. Hitzman, however, does not disclose that the fermentor head comprises a dispensing plate attached to the top of each sample vessel.

Murth discloses a plurality of incubators each comprising a cannula (Figure 1:14) capable of delivering air to the interior of vessel. Each cannula is associated with a main gas supply line (Figure 1:11) located within a dispensing plate (Figure 2:10) located above the array of incubators. This is disclosed in the provided English abstract.

Weuster-Botz discloses a fermentor head comprising a dispensing plate (Figure 1:9) capable of delivering gas to a plurality of arranged sample vessels (Figure 2:1). An air inlet is in communication with the dispensing plate, and the dispensing plate is capable of evenly distributing critical gases to each of the sample vessels. This is disclosed in column 2, line 65 to column 3, line 25.

Hitzman, Murth and Weuster-Botz are analogous art because they are from the same field of endeavor regarding fermentation systems.

At the time of the invention, it would have been obvious to use a dispensing plate to deliver gases through cannulas located above the plurality of sample vessels described in the method of Hitzman. Murth and Weuster-Botz each teach that it is beneficial to use a dispensing plate in this manner as a means to evenly distribute gases to a plurality of fermentors simultaneously. A single dispensing plate is advantageous because it allows for uniform gas or oxygen supply. The operation of the Murth and Weuster-Botz dispensing plates is relatively inexpensive and easily controllable since only a single gas feed line is required (instead of a separate feed line for each sample vessel).

With respect to claims 43 and 64-67, Hitzman and Murth and/or Weuster-Botz disclose the methods set forth in claims 42 and 59 as set forth in the 35 U.S.C. 103 rejections above. In column 4, lines 44-46, Hitzman discloses the use of cylindrical fermentation vessels having volumes as low as 116 ml (0.5 inches in diameter and 3 feet in length). Although Hitzman does not disclose the use of vessels that have capacities lower than 100 ml, it would have been obvious to construct them in this way if it was determined that a collection of smaller bioreactors would have been more efficient in the production cells and cell products. The selection of a bioreactor volume is a result effective variable that is optimized through routine experimentation. See MPEP 2144.05.

With respect to claims 48 and 62, Hitzman and Murth and/or Weuster-Botz disclose the method in claims 42 and 59 wherein air or an oxygen containing gas is added to each of the vessels. Hitzman discloses that aerobic fermentation procedures are well known in the art.

With respect to claims 49 and 50, Hitzman and Murth and/or Weuster-Botz disclose the method in claim 42 wherein gas comprising air and oxygen is added to the samples over time. Since Hitzman teaches that the microorganisms consume oxygen during aerobic fermentation, the ratio of air to oxygen will inherently increase unless heavy sparging is continued. Aerobic fermentation processes that involve a decrease in oxygen concentration levels at various rates as a result of cellular metabolism are well known in the art.

With respect to claim 51, Hitzman and Murth and/or Weuster-Botz disclose the method in claim 42 wherein the sample vessels are arranged in a linear array. This is apparent from Figure 2 of Hitzman.

With respect to claims 77 and 78, Hitzman and Murth and/or Weuster-Botz disclose the methods set forth in claim 59 as set forth in the 35 U.S.C. 103 rejections above. Hitzman teaches in column 5, lines 3-6 that bioreactors are provided as an array of 50 units. Although Hitzman does not expressly disclose the use of an 8 by 12 array or an array that comprises 96, 384 or 1536 vessels, it would have been obvious to rearrange the system of Hitzman in this way if it was determined that 96, 384 or 1536 were needed for a specific operation. Clearly, Hitzman discloses that his system is capable of accommodating a large number of bioreactor units. It

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would require only minor alterations in the method of Hitzman in order to incorporate 96, 384 or 1536 vessels.

With respect to claim 79, Hitzman and Murth and/or Weuster-Botz disclose the method in claim 79 wherein the sample vessels in the container frame are positioned in a water bath designed to control the temperature of the vessels. This is disclosed in column 3, lines 44-47 of Hitzman.

2) Claims 42-51, 53-56, 59-61, 63-67, 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arad (US 5534417) in view of Muth (DE 19712575) and/or Weuster-Botz (US 6063618).

With respect to claims 42 and 59-61, Arad discloses a method of fermenting a plurality of samples wherein a plurality of sample vessels (Figure 1:5 and Figure 1:6) are arranged in a container frame comprising vertical posts (Figure 1:2), a base (Figure 1:3) and horizontal upper element (Figure 1:4). Column 4, lines 50-55 and column 5, lines 11-31 state that a gas is moved through a manifold located inside the horizontal upper element in such a way that the gas is simultaneously delivered to each of the vessels using a plurality of cannulas (Figure 1:7). Although Arad discloses a common gas manifold, Arad does not state that the fermentor head comprises a dispensing plate attached to the top of each sample vessel.

Murth discloses a plurality of incubators each comprising a cannula (Figure 1:14) capable of delivering air to the interior of vessel. Each cannula is associated with a main gas supply line

(Figure 1:11) located within a dispensing plate (Figure 2:10) located above the array of incubators. This is disclosed in the provided English abstract.

Weuster-Botz discloses a fermentor head comprising a dispensing plate (Figure 1:9) capable of delivering gas to a plurality of arranged sample vessels (Figure 2:1). A air inlet is in communication with the dispensing plate, and the dispensing plate is capable of evenly distributing critical gases to each of the sample vessels. This is disclosed in column 2, line 65 to column 3, line 25.

Arad, Murth and Weuster-Botz are analogous art because they are from the same field of endeavor regarding fermentation systems.

At the time of the invention, it would have been obvious to use a dispensing plate to deliver gases through cannulas located above the plurality of sample vessels described in the method of Arad. Murth and Weuster-Botz each teach that it is beneficial to use a dispensing plate in this manner as a means to evenly distribute gases to a plurality of fermentors simultaneously. A single dispensing plate is advantageous because it allows for uniform gas or oxygen supply. The operation of the Murth and Weuster-Botz dispensing plates is relatively inexpensive and easily controllable since only a single gas feed line is required (instead of a separate feed line for each sample vessel).

With respect to claims 43 and 64-67, Arad and Murth and/or Weuster-Botz disclose the methods set forth in claims 42 and 59 as set forth in the 35 U.S.C. 103 rejections above. In column 3, line 65 to column 4, line 5, Arad discloses the use of cylindrical fermentation vessels having volumes as low as 200 ml (5 cm in circumference and 10 cm in length). Although Arad

does not disclose the use of vessels that have capacities lower than 100 ml, it would have been obvious to construct them in this way if it was determined that a collection of smaller bioreactors would have been more efficient in the production cells and cell products. The selection of a bioreactor volume is a result effective variable that is optimized through routine experimentation. See MPEP 2144.05.

With respect to claims 44-47, Arad and Murth and/or Weuster-Botz disclose the method in claim 42 wherein the samples undergo processing following the completion of fermentation. Column 7, lines 32-46 of Arad state that half of the cell solution is withdrawn from the vessels through a fluid outlet (Figure 1:9) and delivered to a conical tank. The cells are allowed to settle and precipitate at the bottom of the tank. The upper fraction from the tank is then returned to the cell solution remaining in the vessels using a recycling technique that involves aspiration (suction).

With respect to claims 48 and 62, Arad and Murth and/or Weuster-Botz disclose the method in claims 42 and 59 wherein air (and therefore oxygen) is added to the samples. This is disclosed in column 5, lines 11-18 of Arad.

With respect to claims 49 and 50, Arad and Murth and/or Weuster-Botz disclose the method in claim 42 wherein gas comprising air and oxygen is added to the samples over time. Since Arad teaches that the algae produce oxygen during their growth, the ratio of air to oxygen will inherently decrease unless heavy sparging of air and carbon dioxide is continued. Plant cell

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culturing processes that involve an increase in oxygen concentration levels at various rates as a result of cellular metabolism are well known in the art.

With respect to claim 51, Arad and Murth and/or Weuster-Botz disclose the method in claim 42 wherein the sample vessels are arranged in either a linear array or a rectangular array. Arad suggests the use of a 4 X 30 array of cells in column 7, lines 13-21.

With respect to claims 53-56, Arad and Murth and/or Weuster-Botz disclose the method in claim 42 wherein the concentration of cells, the concentration of cellular products, and temperature are all monitored throughout the entire culturing process. This is disclosed in column 7, lines 25-46 and column 8, lines 38-42 of Arad. Accordingly, sensors must inherently have been coupled to the sample vessels. The use of environmental control systems during fermentation is considered to be notoriously well known in the art. The detection and estimation of cell concentration in a culture medium is typically accomplished by measuring the optical density of the medium.

With respect to claim 63, Arad and Murth and/or Weuster-Botz disclose the method in claim 59 wherein anaerobic fermentation is accomplished by delivering an inert gas to maintain anaerobic fermentation conditions in the sample vessels. Specifically, Arad teaches that his method is generally used to culture algae cells that do not require oxygen to undertake photosynthesis. Nitrogen gas in the air added to the vessels is an inert gas that maintains anaerobic conditions.

With respect to claims 77 and 78, Arad and Murth and/or Weuster-Botz disclose the methods set forth in claim 59 as set forth in the 35 U.S.C. 103 rejections above. In column 7, lines 13-21, Arad offers an example in which the bioreactors are arranged in a 4 X 30 array. Although Arad does not expressly disclose the use of an 8 by 12 array or an array that comprises 96, 384 or 1536 vessels, it would have been obvious to rearrange the system Arad in this way if it was determined that 96, 384 or 1536 were needed for a specific operation. Clearly, Arad discloses that his system is capable of accommodating a large number of bioreactor units. It would require only minor alterations in the method of Arad in order to incorporate 96, 384 or 1536 vessels.

3) Claims 52, 57, 58 and 68-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hitzman (US 4519984) in view of Muth (DE 19712575) and/or Weuster-Botz (US 6063618) as applied to claims 42 and 59, and further in view of Powell (US 6066497).

With respect to claims 52 and 68-76, Hitzman and Murth and/or Weuster-Botz disclose the method set forth in claims 42 and 59 as set forth in the 35 U.S.C. 103 rejections above, however do not expressly state that the reaction vessels are moved to a processing station that includes a centrifuge and an aspirator head.

Powell discloses a processing station for a plurality of bioreactor vessels (Figure 1:6). The processing station rotates the vessels according to a centrifugal motion about a horizontal axis (Figure 2:4). The vessels are equipped with a distribution assembly capable of sucking fluid from each of the vessels or delivering fluid to the vessels using a plurality of tubes (Figure 1:9). This is disclosed in column 1, lines 39-60 and in column 3, line 64 to column 4, line 67.

Hitzman and Powell are analogous art because they are from the same field of endeavor regarding cell culture apparatuses.

At the time of the invention, it would have been obvious to further process the bioreactor vessels disclosed by Hitzman using the system disclosed by Powell. Powell teaches in column 1, lines 9-35 that subjecting a bioreactor vessel to continuous rotation is beneficial because the rotation serves to facilitate mixing while ensuring that cells remain bathed in the culture medium. The addition and aspiration of liquids to and from a culture vessel during fermentation and during post processing stages is considered to be well known in the art.

With respect to claims 57 and 58, Hitzman and Murth and/or Weuster-Botz disclose the method set forth in claim 42 as set forth in the 35 U.S.C. 103 rejection above. Hitzman, however, does not expressly indicate that the vessels are autoclaved.

Powell discloses the method as previously described above. In addition, Powell teaches in column 7, lines 20-27 that the bioreactor vessels are heat sterilized.

At the time of the invention, it would have been obvious to autoclave the plurality of sample vessels disclosed by Hitzman. Powell indicates that it is important to sterilize bioreactor components prior to fermentation in order to remove an biological contaminants from the system. Autoclaves are considered to be well known in the art as effective means to accomplish heat sterilization.

Response to Arguments

Applicant's arguments filed 07 March 2008 with respect to the 35 U.S.C. 102 rejection involving Hitzman and Arad have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combination of Hitzman with Muth and/or Weuster-Botz and the combination of Arad with Muth and/or Weuster-Botz.

The Murth and Weuster-Botz references each address the deficiencies of Hitzman and Arad. Murth and Weuster-Botz both indicate that fermentor heads comprising a common dispensing plate in communication with a plurality of cannulas are well known in the art. Dispensing plates of this nature are beneficial because they can be used to uniformly and simultaneously deliver critical gases to a plurality of sample vessels.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/William H. Beisner/
Primary Examiner, Art Unit 1797

/Nathan A Bowers/
Examiner, Art Unit 1797